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*Original Research*

# Does polycystic ovarian syndrome increase the risk of congenital anomalies in intracytoplasmic sperm injection cycles?



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**Abstract**

Aim: In this study, we aimed to investigate the effects of polycystic ovary syndrome (PCOS) on the increased risk of congenital anomaly (CA) in intracytoplasmic sperm injection (ICSI) cycles.

Material and Methods: This cross-sectional retrospective study was done on 437 participants who attended our hospital's infertility clinic from January 2019 to January 2020. The participants were divided into two groups: PCOS and normoresponder group (NR). The number of patients was 178 (40.7%) in the PCOS group and 259 (59.3%) in the NR group, respectively. Demographic characteristics and baseline clinical characteristics included maternal age, body mass index (BMI), anti-Mullerian hormone (AMH) level, total gonadotropin dose used, number of retrieved oocytes, metaphase II oocytes.

Results: The mean age of mothers was 30.46 years (±3.99), and the mean BMI was 24.3(±3.2). There is a statistically significant relationship between maternal age and increased CA risk (p-value=0.03). There was also a statistically significant relationship between high AMH levels and increased CA risk (p-value=0.03). AMH levels were significantly higher in the mothers of babies with CA than in mothers of babies without CA. There was a statistically significant relationship between the number of pronuclear oocyte and CA (p-value=0.02). A significant relationship was also found between CA and PCOS (p-value=0.005). The risk of congenital cardiac anomaly (CCA) was significantly higher in the PCOS group than in the NR group (p-value=0.02).

Discussion: We found that the incidence of CA, especially CCA, was higher in PCOS patients. Therefore, women should be informed in ICSI cycles about the increased risk of CA if they had PCOS.

**Keywords**

Congenital anomalies; Intracytoplasmic sperm injection; Normoresponder; Polycystic ovary syndrome

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## Introduction

Congenital anomalies (CA) are defined as any anatomic malformations at birth, which can be diagnosed in approximately 3 to 5% of newborns [1]. The World Health Organization (WHO) reports approximately 3 million infants and fetuses with major CA born every year. They are found in approximately 3% of newborns [2]. CA have risk factors, including 20 to 25% for the interplay of environmental and genetic factors, 10% for environmental exposures, and 15% for chromosomal and genetic factors [3]. Although diagnostic advancements, major CA still cause neonatal deaths in approximately 22% of cases. Individuals may suffer from such malformations as cardiovascular, renal, and pulmonary anomalies later in life, rather than at birth [4]. One of the serious congenital disorders is congenital heart defects (CHD) [5]. Ventricular septal defect (VSD) in the pediatric age group has the incidence of 1-2 out of 1000 live births as the most common CHD [6]. CHD occurs in almost 1% of live births [7]. CHD causes perinatal mortality as the most common form of congenital disorders [8]. Different studies have reported CHD in 0.6-1 for every 100 live births [9]. The etiology of CHD is complex and has not been yet understood well, but it may be caused by hereditary and multifactorial factors, environmental factors such as medicines, infection, maternal diseases [10], one of which may be polycystic ovary syndrome (PCOS). PCOS is the most common endocrine disorder affecting women of reproductive age, leading to infertility and anovulation; 4–12% of women are affected by it [11,12]. Generally,women with PCOS are more obese than those without PCOS. Pregnant women with PCOS may confront a growing risk of pregnancy complications such as hypertensive disorders, gestational diabetes, increased cesarean section rates, and premature delivery. PCOS women's offspring may be at increased risk of congenital abnormalities and may be hospitalized during childhood [13]. In other words, the main pathologies of PCOS contributing to the outcomes include endocrine and metabolic factors related to gestational diabetes mellitus (GDM), leading to CA and premature rupture of membranes (PPROM) [14]. There are limited data to understand the pathophysiological associations between PCOS and pregnancy and delivery outcomes [15]. Therefore, the present study aims to investigate the risk factors of congenital anomaly in PCOS and cardiac abnormalities to see if some variables, i.e., age of mothers, body mass index (BMI), Anti Mullerian hormone (AMH), total oocyte, metaphase II oocyte (MII), pronuclear oocyte (PN), smoking, etc. were associated with general anomaly and cardiac anomaly, and if there is a difference between PCOS and normoresponder (NR) group in terms of these variables and congenital anomalies.

## Material and Methods

This cross-sectional retrospective study was conducted with 437 participants who attended our hospital's infertility clinic from January 2019 to January 2020. This study was approved by the Ethics Committee of Beykoz University, Turkey (No: 2020/3). All procedures conducted in studies, including human participants, were in accordance with the national or institutional research committee's ethical standards and the 1964 Helsinki Declaration and its later amendments or other ethical standards.

The participants were divided into two groups: PCOS and NR group. The total number of patients in the PCOS group was 178 (40.7%) and 259 (59.3%) in the NR group, respectively. Patients with severe male factor, azoospermia, low ovarian reserve, and chronic disease were excluded from the study. Demographic characteristics and baseline clinical characteristics, including the age of the mother, age of the father, BMI, AMH, the total dose of gonadotropin, number of retrieved oocytes, MII oocytes, PN were collected. Those with chronic illnesses and chromosomal abnormalities were excluded from the study. The inclusion criteria were age less than 40 years and 1 or 2 in vitro fertilization (IVF) treatment.

### *Statistical analysis*

Statistical Package for Social Sciences (SPSS) version 26.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistics. Logistic regression was used to assess the factors associated with Anomaly exposure. In this case that we have zero events in a subgroup, penalized maximum likelihood estimation was used. The variables with $P < 0.05$ in the univariate logistic regression analysis were included in the adjusted logistic regressions models.

## Results

This study sample consisted of 437 participants (178 PCOS cases and 259 NR) with a mean age of 30.46 years (±3.99). Table 1 shows the descriptive statistics for the variables. As can be seen from Table 1, the mean age of the mothers was 30.46 years (±3.99), and the mean age of the fathers was 34.7 years (±3.8). The mean BMI of the participants was 24.3 (±3.2). The mean number of IVF trial is 0.93 (±1.1). The mean AMH is 3.4 (±3.5) ng/ml. The total mean gonadotropin used was 2249.3(±516.4) IU. The mean duration of treatment was 10.2 (±0.7) days. The mean number of retrieved oocytes was 9.9 (±5.7). The mean MII and PN were 7.7(4.5) and 7.0892(4.07), respectively. Three hundred forty-four (78.7%) of patients had primary infertility and 93 (21.3%) had secondary infertility. Four hundred twenty subjects (96.1%) did not smoke. Four hundred thirty subjects (98.4%) had no heart anomaly, while 7 subjects (1.6%) had heart anomalies. Four hundred and ten subjects (93.8%) had no congenital anomalies, while 1 subject (0.2%) had congenital hip displacement. Seven subjects (1.6%) had a heart anomaly and 3 subjects (0.7%) had hydrocephalus.

Table 2 shows that the mean age of mothers with anomalous babies was 31.9 (±3.4) years. The mean BMI of the participants with anomalous babies was 25.3 (±4.7). The mean number of IVF trial is 0.7 (±1.2). The mean AMH level was 3.9 (±2.1) ng/ml. The total mean gonadotropin dosage used was 2075 (±433.9) IU. The mean duration of treatment was 10.3 (±0.6) days. The mean number of retrieved oocytes was 11.7 (±6.4). The mean number of MII and PN were 9.4 (±5.3) and 8.8 (±4.4), respectively. The number of patients in the PCOS group was 160 (39%), and in the normoresponder group was 250 (61%), respectively. Three hundred and twenty subjects (78%) had primary infertility; 90 subjects (22%) had secondary infertility. Three hundred ninety-three subjects (95.9%) did not smoke.

There is a statistically significant relationship between maternal age and the risk of congenital anomaly (p-value=0.03).

**Table 1.** Descriptive Statistics of variables

| Variable | N | Minimum | Maximum | Mean | Sd |
|---|---|---|---|---|---|
| Age of Mother (y) | 437 | 21 | 39 | 30.46 | 3.99 |
| Age of Father (y) | 437 | 26 | 63 | 34.7 | 4.6 |
| BMI (kg/m2) | 437 | 18 | 49 | 24.7 | 3.2 |
| Number of IVF trial (n) | 437 | 0 | 2 | 0.93 | 1.1 |
| AMH (ng/mL) | 437 | 1.1 | 16 | 3.4 | 3.5 |
| Total gonadotropin use (U) | 435 | 750 | 4500 | 2249.3 | 516.4 |
| Duration of treatment (d) | 437 | 8 | 13 | 10.2 | 0.7 |
| Total oocytes (n) | 437 | 5 | 36 | 9.9 | 5.7 |
| MII (n) | 437 | 4 | 25 | 7.7 | 4.5 |
| PN (n) | 437 | 3 | 22 | 7.0892 | 4.07 |
| | | Frequency | | Percent | |
| Group | | | | | |
| NR | | 259 | | 59.3 | |
| PCOS | | 178 | | 40.7 | |
| Inf. Types | | | | | |
| 1 | | 344 | | 78.7 | |
| 2 | | 93 | | 21.3 | |
| Smoking | | | | | |
| No | | 420 | | 96.1 | |
| Yes | | 17 | | 3.9 | |
| Anomaly (Heart) | | | | | |
| No | | 430 | | 98.4 | |
| Yes | | 7 | | 1.6 | |
| Anomaly (Others) | | | | | |
| No | | 410 | | 93.8 | |
| Congenital Hip Displacement | | 1 | | 0.2 | |
| Heart | | 7 | | 1.6 | |
| Hydrocephalus | | 3 | | 0.7 | |
| Hydrocele | | 2 | | 0.5 | |
| Bone | | 2 | | 0.5 | |
| Kidney | | 9 | | 2.1 | |
| Ear Agenesia | | 1 | | 0.2 | |
| Omphalocele | | 1 | | 0.2 | |
| Cleft lip and cleft palate | | 1 | | 0.2 | |
| Anomaly (Total) | | | | | |
| No | | 410 | | 93.8 | |
| Yes | | 27 | | 6.2 | |

Those women who had a baby with CA were older than those who did not have a baby with CA. There is also a statistically significant relationship between AMH and congenital anomaly (p-value=0.03). The subjects with CA had higher AMH than those without CA. There is a statistically significant relationship between PN number and the risk of congenital anomaly (p-value=0.02). The subjects with anomalies had a higher PN than those without anomaly.

The results of the Kolmogorov test show that not all quantitative variables had a normal distribution. Table 3 examines the relationship between the studied variables and the anomaly variable using the Mann-Whitney. Table 3 shows that there is a statistically significant difference between the PCOS and NR groups in terms of CA (p-value=0.005). In the PCOS group, 18 (66.7%) participants had CA, while 9 (33.3%) participants in the NR group had CA, indicating a significant relationship between CA and PCOS.

**Table 2.** Descriptive statistics of the women with babies with congenital anomaly

| Variable | N | Minimum | Maximum | Mean | Sd |
|---|---|---|---|---|---|
| Age of Mother (y) | 27 | 25 | 37 | 31.9 | 3.4 |
| Age of Father (y) | 27 | 27 | 44 | 35.3 | 3.8 |
| BMI (kg/m2) | 27 | 19. | 45 | 25.3 | 4.7 |
| Number of IVF trial (n) | 27 | 0 | 4 | 0.7 | 1.2 |
| AMH (ng/mL) | 27 | 2 | 10 | 3.9 | 2.1 |
| Total gonadotropin use (U) | 27 | 1000 | 3000 | 2075 | 433.9 |
| Duration of treatment (d) | 27 | 9 | 11 | 10.3 | 0.6 |
| Total oocytes (n) | 27 | 3 | 31 | 11.7 | 6.4 |
| MII (n) | 27 | 3 | 22 | 9.4 | 5.3 |
| PN (n) | 27 | 3 | 18 | 8.8 | 4.4 |
| | | Frequency | | Percent | |
| Group | | | | | |
| NR | | 250 | | 61 | |
| PCOS | | 160 | | 39 | |
| Inf. Types | | | | | |
| 1 | | 320 | | 78 | |
| 2 | | 90 | | 22 | |
| Smoking | | | | | |
| No | | 393 | | 95.9 | |
| Yes | | 17 | | 4.1 | |
| Result | | | | | |
| Negative | | 149 | | 36.3 | |
| Positive | | 261 | | 63.7 | |

**Table 3.** The relationship between the studied variables and anomaly variable

| Variable | Congenital Anomaly (CA) | | p-value |
|---|---|---|---|
| | No | Yes | |
| Group | | | |
| NR | 250(61) | 9(33.3) | 0.005 |
| PCOS | 160(39) | 18(66.7) | |
| Infertility Type | | | |
| 1 | 320(78) | 24(88.9) | 0.1 |
| 2 | 90(22) | 3(11.1) | |
| Smoking | | | |
| No | 393(95.9) | 27(100) | 0.6 |
| Yes | 17(4.1) | 0 | |
| Result | | | |
| Negative | 149(36.3) | 0 | 0.000 |
| Positive | 261(63.7) | 27(100) | |

Anomaly Yes and No means whether there is a congenital anomaly or not.

The relationship between qualitative variables and Cardiac Anomaly was determined using Fisher's exact test. There was a statistically significant relationship between maternal age and CCA (p-value=0.03). There was no statistically significant relationship between other studied variables and CCA (p>0.05). There was a statistically significant relationship between cardiac anomaly and the PCOS group (p-value=0.02). Six subjects in the PCOS group had an anomaly, and one subject in the NR group had CCA. The results show that CCA was more common in the PCOS group. Two subjects in the PCOS group had VSD, while one subject in the NR group had VSD. Three subjects in the PCOS group had tetralogy of Fallot (TOF), while

no subjects in the NR group had TOF. One subject in the PCOS group had atrial septal defect (ASD)-VSD, while no subject in the NR group had ASD-VSD. TOF was the most common heart anomaly in the PCOS group.

## Discussion

The aim of the present study was to investigate the risk factors for congenital anomaly and the cardiac anomaly in the PCOS to see if some variables, i.e., maternal age, BMI, AMH, total oocyte, MII, PN, smoking were associated with CA and CCA and if there was a difference between PCOS and normoresponder group in terms of these variables and CA and CAA. The findings show that those who had the CA and CCA were older than those who did not have anomalies. The subjects with anomalies had higher AMH levels than those without anomaly. The subjects with anomalies had higher PN number than those without anomaly. The number of subjects in the PCOS group with CA was higher than that of the NR group. In other words, PCOS is associated with an increased risk of CA. Increased maternal age was also associated with an increased cardiac anomaly risk. Two subjects in the PCOS group had VSD, while one subject in the NR group had VSD. Three subjects in the PCOS group had TOF, while none of the subjects in the NR group had TOF. One subject in the PCOS group had ASD-VSD, while none of the subjects in the NR group had ASD-VSD. TOF was the most common heart anomaly in the PCOS group.

Maternal age significantly affects the congenital malformation of the fetus [16]. Studies in Turkey show that 5.2% of the mothers are over 35 years old [17], while older mothers had 8.7% of anomalous births, but this was not statistically significant [16]. Their result is in line with the results of our study, but not in line with the results of the study by Francine et al. Francine et al. also found that congenital cardiovascular anomalies (16.6%) and limb anomalies were the most common ones in their study [18]. The studies on singleton pregnancies showed that PCOS women are older, have early pregnancy, need ART to conceive, and have a higher BMI than those without PCOS [19]. In older women, CCA has more risk factors, such as poor oocyte quality, infections, autoimmune diseases, pre-gestational diabetes, uterine aging drug exposure, or other causes of infertility [8]. Most women with PCOS are overweight or obese, and a higher risk of preterm delivery was observed in overweight and obese women during pregnancy, as reported by a recent study [20], and obesity is metabolically associated with PCOS [11]. Liu et al. found an association between pregravid obesity and an increased risk of adverse pregnancy outcomes after adjusting the variations of parity, PCOS, maternal age, etc. There was an association between obesity and congenital anomalies, and that PCOS had endocrine and metabolic effects on the GDM, contributing to congenital anomalies [14]. Our study found that BMI in the women with anomaly was higher than that in those without anomaly, but this association was not significant, but found that PCOS could significantly contribute to the congenital anomalies. Our study found that VSD and TOF were the most common cardiac anomaly in the groups. TOF was common in only the subjects with PCOS, while VSD was common in both groups, which is in line with the results of the study by Kirklin et al. [6], who found that VSD is the most common congenital anomaly. Francine et al. found that limb anomalies (16.6 %), including abnormal palmar crease (4.16%) and polydactyly (12.2%) and congenital cardiovascular anomalies (16.6%), were observed in most malformed stillbirths [18]. Mills et al. [21] found that those with PCOS more likely to have infants with congenital anomalies than those without PCOS, which is in line with our study results. Doherty et al. [22] also found that cardiovascular and urogenital malformations were more common in children of women with PCOS, supporting our study findings. Hart [12] found impairment of the glucostasis for some women with PCOS, leading to intergenerational influence that is not immediately detected during pregnancy, resulting in a higher risk of cardiometabolic and congenital malformations for the offspring.

### *Conclusion*

It is concluded that PCOS was significantly associated with an increased risk of CA and CCA. The subjects with anomalies had higher age, AMH level and PN numbers than those without anomaly. Therefore, women should be informed about the increased risk of CA if they had PCOS.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and human rights statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

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***Conflict of interest***

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***References***

*1. Ahmadzadeh A, Safikhani Z, Abdulahi M, Ahmadzadeh A. Congenital malformations among live births at Arvand Hospital, Ahwaz, Iran: A prospective study. Pakistan J Med Sci. 2008; 24(1):33.*

*2. Kalter H, Warkany J. Medical progress. Congenital malformations: etiologic factors and their role in prevention (first of two parts). N Engl J Med. 1983; 308(8):424-31.*

*3. Rahbar M, Ahmadi M, Lornejad HR, Habibelahi A, Sanaei-Shoar T, Mesdeaghinia AR. Mortality causes in children 1–59 Months in Iran. Iran J Pub Health. 2013; 42(1):93.*

*4. Parmar A, Rathod SP, Patel SV, Patel SM. A study of congenital anomalies in newborn. NJIRM. 2010; 1(1):13-7.*

*5. Lin AE, Herring AH, Amstutz KS, Westgate MN, Lacro RV, Al-Jufan M, et al. Cardiovascular malformations: Changes in prevalence and birth status, 1972–1990. Am J Med Genet. 1999; 84:102-10.*

*6. Kirklin JW, Barratt-Boyes BG. Cardiac surgery, 2nd ed. New York: Churchill Livingstone; 1993. p.750-1.*

*7. Hoffman J, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002; 39(12):1890-900.*

*8. Giorgione V, Parazzini F, Fesslova V, Cipriani S, Candiani M, Inversetti A, et al. Congenital heart defects in IVF/ICSI pregnancy: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018 ;51(1):33-42.*

*9. Hoffman JIE. Incidence of congenital heart disease: I. Post¬natal incidence. Pediatr Cardiol 1995;16:103-13.*

*10. Rose V, Gold RJM, Lindsay G, Allen M. A possible increase in the incidence of congenital heart defect among the offspring of affected parents. J Am Coll Cardiol. 1985; 6(2):376-82.*

*11. Costello MF, Misso ML, Wong J, Hart R, Rombauts L, Angela Melder A, et al. The treatment of infertility in polycystic ovary syndrome: a brief update. Aust N Z J Obstet Gynaecol. 2012; 52(4):400-3.*

*12. Hart R, Hickey M, Franks S. Definitions, prevalence and symptoms of polycystic ovaries and polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol. 2004; 18(5):671-83.*

*13. Joham AE, Palomba S, Hart R. Polycystic ovary syndrome, obesity, and*

*pregnancy. Semin Reprod Med. 2016; 34(2): 93-101.*
*14. Liu L, Wang H, Zhang Y, Niu J, Li Z, Tang R. Effect of pregravid obesity on perinatal outcomes in singleton pregnancies following in vitro fertilization and the weight-loss goals to reduce the risks of poor pregnancy outcomes: A retrospective cohort study. Plos One. 2020; 15(2):e0227766. DOI: 10.1371/journal.pone.0227766.*
*15. Khomami MB, Boyle JA, Tay CT, Vanky E, Teede HJ, Joham AE, et al. Polycystic ovary syndrome and adverse pregnancy outcomes: current state of knowledge, challenges and potential implications for practice. Clin Endocrinol. 2018; 88:761-69.*
*16. Hollier LM, Leveno KJ, Kelly MA, MCIntire DD, Cunningham FG. Maternal age and malformations in singleton births. Obstet Gynecol. 2000; 96(5 Pt 1):701-6.*
*17. Studies HUIoP. Turkey Demographic and Health Survey 2003. In: Hacettepe University Institute of Population Studies MoHGDoMaCHaFP, State Planning Organization and European Union, editor. Ankara, Turkey, 2004.*
*18. Francine R, Pascale S, Aline H. Congenital anomalies: prevalence and risk factors. Journal of Public Health. 2014; 2(2):58-63.*
*19. Løvvik TS, Wikström AK, Neovius M, Stephansson O, Roos N, Vanky E. Pregnancy and perinatal outcomes in women with polycystic ovary syndrome and twin births: a population-based cohort study. BJOG. 2015; 122(10):1295-302.*
*20. Cnattingius S, Villamor E, Johansson S, Edstedt Bonamy AK, Persson M, Wikstrom AK, et al. Maternal obesity and risk of preterm delivery. JAMA. 2013; 309(22):2362–70.*
*21. Mills G, Badeghiesh A, Suarthana E, Baghlaf H, Dahan MH. Associations between polycystic ovary syndrome and adverse obstetric and neonatal outcomes: a population study of 9.1 million births. Hum Reprod. 2020;35(8):1914-21.*
*22. Doherty DA, Newnham JP, Bower C, Hart R. Implications of polycystic ovary syndrome for pregnancy and for the health of offspring. Obstet Gynecol. 2015; 125(6):1397–406.*
*23. Hart R. Generational Health Impact of PCOS on Women and their Children. Med Sci (Basel). 2019; 7(3):49.*

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